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P H Y S I C I A N S

## Inhaled Corticosteroids for Asthma Therapy\* Patient Compliance, Devices, and Inhalation Technique

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**Background:** Patient compliance, inhalation devices, and inhalation techniques influence the effectiveness of inhaled medications.  
**Methods:** This article presents the results of a systematic literature review of studies measuring compliance with inhaled corticosteroids, measuring inhalation technique with different inhalation devices, and estimating the proportion of inhaled drug that is deposited in the lung.  
**Results:** Overall, patients took the recommended doses of inhaled medication on 20 to 75% of days. Frequency of efficient inhalation technique ranged from 46 to 59% of patients. Education programs have been shown to improve compliance and inhalation techniques. The lung deposition achieved with different inhalers depends on particle size as well as inhaler technique.  
**Conclusion:** This review demonstrates that multiple factors may come between a prescription of an inhaled corticosteroid and the arrival of that medicine at its target organ, the lung.  
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**Key words:** asthma; compliance; inhaler technique; inhalers

**Abbreviations:** DPI = dry powder inhaler; ICS = inhaled corticosteroid; MDI = metered-dose inhaler

Asthma is a common chronic inflammation of the airways that causes periodic attacks of wheezing and troubled breathing. Pharmacologic therapy is used to prevent and control asthma symptoms and reverse airflow obstruction. The major classes of asthma medications are  $\beta$ -agonists, methylxanthines, anticholinergics, leukotriene modifiers, inhaled corticosteroids, and corticosteroids (glucocorticoids). The majority of these medications are inhaled, and their effectiveness in clinical practice can be affected by many factors.

In this article, we examined three factors that appear to have an effect on the effectiveness of inhaled corticosteroid (ICS) treatment by conducting a review of the relevant literature. First, we

examined patient compliance with inhaled asthma therapy. Second, we examined inhalation technique. Third, we examined the impact of inhalation technique and inhalation device on drug deposition in the lungs. The main objective of the article was to summarize the research conducted so far into these three factors to provide information about the reliability of the inhaled route of administration of ICSs.

### MATERIALS AND METHODS

The literature review started with a thorough key word search of the National Library of Medicine's MEDLINE database for articles on inhaled asthma therapy published between January 1986 and 1997. We examined the abstracts of these articles and identified articles that presented the results of studies of compliance, inhalation technique, and lung deposition of inhaled asthma drugs. We obtained these articles and examined their references for any other articles pertaining to these issues. We identified Australian and European articles from journals that are included in MEDLINE, such as *European Respiratory Journal*, *Medical Journal of Australia*, *Australian and New Zealand Journal of Medicine*, *European Journal of Respiratory Diseases*, and *Acta Allergologica*, as well as from international medical journals such as *Lancet*, *Asthma*, and *Respiratory Medicine*. From searching the references of the articles we obtained with the MEDLINE search, we found articles from European journals not listed in MEDLINE, such as *British Journal of Disease of the Chest*. In

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Table 2—Proper Inhalation Technique\*

Study	No.	Year	Trained	Type of Inhaler	Physician Assessment, %		Frequency of Efficient Technique, %
					Good	Inadequate	
Dowling et al. <sup>1</sup>	41	1992	Yes	Rotahaler	5	95	27
Hillman <sup>20</sup>	62	1990	NS	Rotahaler	30	29	21
Pedersen et al. <sup>21</sup>	39	1996	Yes	Rotahaler	45	25	30
Hillman <sup>20</sup>	252	1990	NS	MDI	45	25	30
Crompton <sup>22</sup>	132	1996	Yes	MDI	6	40	51
Pedersen et al. <sup>21</sup>	86	1995	No	MDI	46	29	15
Honley and Bailey <sup>23</sup>	86	1995	Yes	MDI	86	6	8
Honley and Bailey <sup>23</sup>	321	1976	Yes	MDI	28	13	59
Pedersen and Crompton <sup>24</sup>	69	1990	No	MDI	52	11	37
Cayard and Oreluck <sup>25</sup>	46	1990	Yes	MDI	58	20	22
Wilton <sup>26</sup>	35	1990	NS	Spacer device	78	18	4
Pedersen et al. <sup>21</sup>	85	1996	Yes	Rotahaler	54	27	19
Hillman <sup>20</sup>	26	1990	NS	Rotahaler	54	27	19

\*NS = not specified.

†The study's categories were reclassified as follows: failless = good; doubtful or adequate = adequate; totally inadequate or probably inadequate = inadequate.

‡The study's categories were reclassified as follows: efficient = good; doubtful = adequate; inefficient = inadequate.

§The study's categories were reclassified as follows: correct = good; doubtful = adequate; incorrect = inadequate.

Melchor et al.<sup>25</sup> showed an increase in peripheral lung deposition of salbutamol, but not in total lung deposition, with the use of a spacer device.

Proper inhalation technique can also significantly affect the amount of drug delivered to the lung. Newman et al.<sup>26</sup> showed that for patients who could not coordinate inhalation and actuation at baseline (44% of the population), instruction improved lung deposition from 7.2 to 22.8%. Furthermore, before instruction, the patients who coordinated inhalation and actuation had a higher lung deposition (18.6%) than those who did not (7.2%).

## DISCUSSION

In this paper, we examined three factors influencing the effectiveness of asthma treatment with ICSs in practice—patient compliance, inhalation technique, and lung aerosol deposition. We found that only a small percentage of the prescribed dose of an ICS is likely to reach the target organ, the lung, because of patient noncompliance with the prescribed dose, difficulty in correct use of the inhaler, and the ability of a properly used inhaler to deliver the drug to the lung.

As with any chronic disease, patient compliance is an important determinant of therapeutic success. Greer and Levstek<sup>27</sup> divide the factors that are correlated with noncompliance into four categories: patient variables, interactions between

physician or medical staff and patients or family, medication characteristics, and nature of asthma. Our evaluation indicates that patients were more likely to underuse ICSs than overuse them. Some examples of factors related to noncompliance and inhaled drugs include patients taking long-term medication who stop treatment if they have not experienced an attack for an extended period.<sup>28</sup> The delayed clinical impact of ICSs compared with bronchodilator drugs may be an additional factor in noncompliance. The possibility of psychosocial issues in noncompliant patients should not be overlooked. Bosley et al.<sup>29</sup> found in a prospective cohort that noncompliant patients had a significantly higher prevalence of depression than compliant patients. Noncompliant patients also had a higher, although not statistically significant, prevalence of anxiety.

There is conflicting evidence about the relationship between the number of inhalations prescribed per day and compliance rates. Two published studies supported the assumption that there is an inverse relationship between the number of inhalations prescribed per day and compliance.<sup>17,41</sup> However, this inverse relationship was not supported in studies by Bosley et al.<sup>29</sup> and Toogood et al.<sup>42</sup>

Education has been shown to increase compliance with dosing regimens. The study by van der Walen et al.<sup>14</sup> showed this using electronic monitoring for compliance. A recent meta-analysis of the effects of

Table 3—Observed Errors in Inhalation Checklists\*

Factors	MDI									
	Pedersen et al. <sup>21</sup>	Pedersen et al. <sup>21</sup>	van Berendse et al. <sup>20</sup>	Manzella Epstein et al. <sup>22</sup>	Honley et al. <sup>23</sup>	Scott et al. <sup>24</sup>	Smith et al. <sup>25</sup>	1st Puff et al. <sup>26</sup>	2nd Puff et al. <sup>26</sup>	Cayard and Oreluck <sup>25</sup>
Number of patients	132	851	56	34	65	84	20	19	59	69
Release cap, %	49	34	57	15	29	32	18	10	32	46
Shake inhaler, %			2		4	5	0	0	0	
Hold inhaler upright, %					12					
Place mouthpiece of inhaler into one end of spacer, %					19					
Position inhaler with index finger on top and thumb supporting the bottom, %					19					
Exhale before firing, %	45	51	66		58	0	15	26	75	41
Tilt head back, %	12	14			15	30				
Place spacer tube between teeth, %					25	13		0	0	
Close mouth, %					16					
Release medication, %	55	17	68		34	40	25	42	47	33
Begin to breathe in and then activate inhaler, %	67	29	70		43	45	40	47	39-42	41
Inhale slowly and deeply, %	42	39	53		31	66	59	32	24	
Hold breath, %					75					
Breathe out through nose, %					49		20	32		
Breath released slowly, %					54	23	46	35	NA	
Wait before taking next puff, %										

\*Other Inhalers

Factors	Other Inhalers									
	Pedersen et al. <sup>21</sup>	van Berendse et al. <sup>20</sup>	Dowling et al. <sup>1</sup>	1st Puff et al. <sup>26</sup>	2nd Puff et al. <sup>26</sup>	Wilton <sup>26</sup>				
Number	39	257	41	13	14	144				
Type of Inhaler	Rotahaler	Mix of dry powder inhalers	Rotahaler	Rotahaler	Rotahaler	Turbuhaler				
Cover removed, %	15	14	0	0	0	2				
Loading drug substance, %		7	51	15	0	0				
Hold inhaler at correct angle, %	46		0	0	0	3				
Rotation sequence correct, %	19					1				
Air fully inhaled, %	62	66	83	0	0	3				
Exhale before firing, %	13		17	0	14	3				
Tilt head back, %	36			15	0					
Drug capsule not emptied, %		4		15	0					
Place mouthpiece between lips, %				15	0					
Release medication, %	41	10	29	23	0	4				
Inhale slowly and deeply, %	49	53	76	23	14					
Hold breath, %				23	14					
Breathe out through nose, %				23	14					
Breath released slowly, %				23	14					
Wait before repeating step, %				8	14					

\*If blank, error was not reported. NA = not applicable for second puff.

†After instruction, others are preinstruction.

psychoeducational care in adults with asthma by Devine<sup>43</sup> also showed improvements in self-reported and physician-assessed compliance associated with education programs.

Other routes of administration for anti-asthma drugs may improve compliance. Kelloway et al.<sup>44</sup> found that compliance was higher with prescribed oral medications compared with inhaled anti-inflam-

matory medications for asthma. However, their study was a retrospective database study that compared oral theophylline with two inhaled anti-inflammatory medicines. Thus, in their study, higher compliance with the oral drug might have been related to more rapid impact of theophylline on symptoms rather than the mode of administration. It is also important to note that oral medications are not affected by two of the three factors discussed in this paper that may reduce drug effectiveness: inhalation technique and lung deposition. Well-designed prospective studies comparing oral and inhaled asthma therapies could help further to determine the importance of route of administration.

Evidence suggests that noncompliance has an effect on patient outcomes. For example, Horn et al<sup>48</sup> treated 160 patients for as long as 9 months with increasing doses of inhaled salbutamol and beclomethasone dipropionate. The authors found that patients whose conditions improved had higher urinary salbutamol concentrations compared with those with persistent problems.

The effectiveness of inhaler therapy also depends on the inhaler technique. Patients may not be adequately instructed in inhaler technique, thereby reducing the amount of drug delivered to the lungs.<sup>30</sup> Cochrane<sup>49</sup> states that "it is important to reinforce the simple concept that failure to instruct patients on how to use inhalers and to reinforce these instructions will decrease compliance, whatever the drug or inhalation device." Our study found that subjective assessments of inha-

tion technique by physicians provided a wide range of values in patients using the inhaler properly. Technique is highly dependent on the type of inhaler. In our evaluation, we found that patients using a Rotahaler and an MDI had similar rates of "inadequate" technique. However, patients using DPIs other than the Rotahaler, such as the Turbuhaler and the Diskhaler, had lower rates of "inadequate" technique. DPIs... have the intrinsic advantage that there is a natural coordination between generation of the aerosol cloud and inspiration.<sup>46</sup> The lack of need for coordination of two activities by the patient using a DPI makes it more likely that their inhalation technique with these devices will be good. As expected, patient groups using a spacer in addition to an MDI had lower rates of "inadequate" technique than the majority of patient groups using an MDI alone.

Because physician rating of patient technique is subjective, other methods of evaluating patient technique are needed, particularly so that the measurement scale can be consistent across studies. The study by Goodman et al<sup>50</sup> is an example of a study using an objective technique for measuring inhaler skills, a computer sensing device.

Several studies have shown that education can have a large impact on the percentage of patients who use an inhaler correctly.<sup>51,52</sup> The study by Goodman et al<sup>50</sup> using a computer sensing device, indicated that women may have a greater need for education on inhaler technique because of less ef-

Table 4—Drug Delivered to Target Area: MDI\*

MDI		MDI With Spacer	
Study	Drug MMD, $\mu$ m	Study	Drug MMD, $\mu$ m
Dolovich et al <sup>12</sup> (n = 127)	Label 2.21	Newman et al <sup>13</sup> (n = 9)	Label 3.2
Newman et al <sup>13</sup> (n = 9)	Label 3.21	Melchor et al <sup>14</sup> (n = 91)	Salbutamol 2.5-3.9
Newman et al <sup>14</sup> (n = 19)	Salbutamol		
Melchor et al <sup>15</sup> (n = 217)	Salbutamol 2.5-2.9		
Zainudin et al <sup>16</sup> (n = 9)	Salbutamol + label 2.3		
Bongers et al <sup>17</sup> (n = 13)	Terbutaline, not specified		
Range		Range	
	7-23		19-21

\*MMD = mass median diameter for inhaled particles.

<sup>†</sup>Based on a maximum of 6.8% delivered to the right lung.

<sup>‡</sup>Label refers to a radioisotope attached to a nontherapeutic particle.

<sup>§</sup>For patients who could not coordinate inhalation and actuation, before and after instruction.

<sup>||</sup>For patients who could not coordinate inhalation and actuation, before and after instruction.

<sup>¶</sup>Range for asthma patients in healthy subjects.

Table 5—Drug Delivered to Target Area: Inhalers\*

Breath-Actuated Inhaler		DPI	
Study	Drug MMD	Study	Drug MMD, $\mu$ m
Newman et al <sup>14</sup> (n = 13)	Salbutamol, not specified	Melchor et al <sup>15</sup> (n = 29)	Salbutamol
		Zainudin et al <sup>16</sup> (n = 9)	Salbutamol + label 2.3
		Bongers et al <sup>17</sup> (n = 10)	Beclomethasone 2.5-3.9
		Bongers et al <sup>17</sup> (n = 13)	Terbutaline, not specified
Range		Range	
	18-21		11-121

\*MMD = mass median diameter for inhaled particles.

<sup>†</sup>Range for patients who could coordinate inhalation and actuation and those who could not after all were trained to use the autohaler.

<sup>‡</sup>Range for asthma patients and healthy subjects.

<sup>§</sup>Label refers to a radioisotope attached to a nontherapeutic particle.

<sup>||</sup>Range for slow to fast inspiratory flow.

<sup>¶</sup>Range based on inhaled drug dose.

fective use of the inhaler. They suggest that this problem with inhaler technique might explain why women experience more severe asthma symptoms than men. However, a recent study in a health maintenance organization population by Osborne et al<sup>47</sup> showed that women had more severe asthma symptoms but that their MDI technique was no different from that of the men when skills were ranked using a 10-item checklist. Osborne et al<sup>47</sup> suggest one possible reason for the difference in results could be that the electronic sensor is a more accurate measure of inhaler skills than the 10-item checklist.

Studies have shown that written instructions are not sufficient and that verbal instructions and demonstrations and practice sessions need to be included.<sup>50</sup> Simple teaching devices can be built to develop coordination skills needed with MDIs.<sup>48</sup> Patients also need to be checked periodically to make sure that their skills have not eroded over time.<sup>50</sup>

The goal of inhaled therapy is to deliver medication directly to the lungs. The patient is at an advantage if the amount of the drug reaching the lungs is maximized and the amount deposited on the oropharyngeal region is minimized. The likelihood of adverse events can be reduced by reducing the amount of drug that reaches the oropharynx.<sup>49</sup> Many factors affect the amount of drug that reaches the lung, including inhaler technique and inhaler type, fine particle dose, and particle distribution. Of the studies in our analysis, only about 7 to 23% of any drug delivered by an MDI enters the respiratory tract. The rest of the drug is either deposited in the oropharynx or swallowed, leading to potential systemic side effects. Studies have shown that the amount of drug delivered to the

lungs can be almost doubled and that the amount of drug deposited in the oropharynx greatly reduced through the use of large-volume spacers.<sup>15</sup> A study using the Turbuhaler showed an increased in drug deposition in the lung.<sup>37</sup> Jackson and Lipworth<sup>13</sup> report two studies that have shown that the use of a Turbuhaler is associated with greater efficacy of ICSs. Thus, the increased deposition might be associated with increased drug efficacy.

The lung deposition studies reported in our article show mixed results and do not clearly demonstrate that one type of inhaler is superior to another for use with ICSs. There is a need for more research in this area. Lung deposition depends critically on particle dynamics and jet flow,<sup>50</sup> which vary with drug formulation, inhaler type, and patient inhaler technique. Large crossover studies will need to be designed that control for drug type and particle size as well as inhaler technique. The outcomes of such studies should be both direct measures of drug deposition as well as measures of patient outcomes.

A key to efficacy for ICSs for treatment of asthma is the amount of drug prescribed that reaches the target organ. This review of patient compliance, inhalation technique, and inhaler type demonstrates the importance of these three factors in the appropriate delivery of ICSs to the lung. Health-care providers should consider these factors when evaluating and prescribing asthma medications.

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